

Topic 02 – Heart failure and cardiomyopathy

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091

Genetic analysis in independent patients with left ventricular non compaction: yield of mutation screening and identification of RBM20 as a new gene involved in the disease

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Background: Left ventricular non compaction (LVNC) is a cardiomyopathy characterized by an excessively prominent trabecular meshwork and deep intertrabecular recesses. Some mutations have been described as responsible for LVNC but the precise prevalence of the related genes and the impact of mutation screening in clinical practice are poorly understood.

Objective: To assess in a cohort of patients with LVNC the prevalence of mutations in three genes previously involved in LVNC (MYH7, TAZ, LDB3) and in two candidate-genes not reported until now (NKX2.5 and RBM20), whatever the familial context.

Methods: Blood DNA was extracted from a population of 59 consecutive patients with a definitive diagnosis of LVNC (Echo core lab), from the French registry of LVNC. The coding exonic sequences and intron-exon boundaries were amplified by PCR and analyzed by HRM (High resolution melting). Profiles suggestive of a variant were sequenced with ABI Prism 3100 Genetic Analyzer. The suspected mutations were genotyped in a control population (>240 chromosomes); segregation within the families were analysed when available; inter-species conservation was analysed after multiple protein sequence alignment.

Results: We identified five mutations in MYH7 gene, two new missense mutations in the TAZ gene (Phe128Ser and Met155Val), no mutation in the LDB3 gene (but two new genetic polymorphisms), one genetic variant of unknown significance in NKX2.5 gene, and two mutations in RBM20 gene.

The total yield of mutation screening was 9/59 (15%), and was similar in sporadic and familial cases.

Conclusion: Mutations are identified whatever the familial context and MYH7 gene is the most frequent gene involved in LVNC in our cohort. We identified RBM20 gene as a new gene involved in LVNC. These findings may have impact for the management of LVNC patients and relatives in clinical practice, including family cardiac screening and mutation screening.

092

Left ventricular systolic dysfunction in tako-tsubo cardiomyopathy: is it transmural and really regional and reversible? A two-dimensional speckle tracking echocardiographic study

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Objective: typical tako-tsubo cardiomyopathy (TT) is characterized by a transient mid-apical left ventricular (LV) systolic dysfunction assessed by the wall motion score (WMS) and LV ejection fraction (EF). Two-

dimensional strain by speckle tracking echocardiography (2DS) is a more sensitive marker of LV systolic function. Our aim was to assess systolic LV mechanics at all myocardial directions (MD) by 2DS, in patients (pts) with TT.

Methods: 2DS was performed in 15 consecutive pts with TT (78±8 years, 93% women, mean LVEF 45±10%), at the acute phase (ap) (within 24 h after symptom onset) and after recovery. 15 control (C) pts matched for age and sex (mean LVEF 71±7%), were compared to TT pts. From the apical long-axis, 4-and 2-chamber views, global longitudinal strain (LS) and strain-rate (LSR), post-systolic shortening index (PSS), and from the parasternal basal, mid and apical short-axis planes, global circumferential strain (CS), and strain-rate (CSR), and radial strain (RS), were obtained. LV twist was defined as the net difference in degrees of apical (Ar) and basal rotation.

Results: At the ap, global LS, LSR, CS, CSR, RS, Ar, and LV twist were significantly reduced, and PSS was higher when compared to C (all, $p < 0.01$). In pts with TT, there was an apex to base gradient of strain and strain-rate at all MD (all, $p < 0.05$), and a significant correlation was found between the WMS, LVEF, and LS, LSR, CS, CSR, RS, LV twist (all, $p < 0.05$), between troponine peak and LV twist, and CSR (all, $p < 0.01$), and between NT-proBNP and CS, CSR, LS, LSR, RS, LV twist (all, $p < 0.05$). At follow-up, in addition to a significant improvement of mid and apical LV mechanics at all MD (all, $p < 0.01$ vs. acute phase), with final values not significantly different from C (all, $p = \text{NS}$), there was a significant improvement of basal CSR, LS, and LSR (all, $p < 0.05$ vs. acute phase).

Conclusion: There is a transmural extent of myocardial impairment in TT, which is correlated to LV wall stress, and is entirely reversible. Furthermore, there are transient subtle abnormalities at the basal level, challenging the notion that LV systolic dysfunction in TT is wholly regional.

093

Tako-tsubo cardiomyopathy: direct evidences of sympathetic nervous system hyperactivity

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Tako-Tsubo Cardiomyopathy (TTC) is an acute reversible condition that involves left ventricular apical 'ballooning' and mimics acute myocardial infarction with no detectable coronary arterial disease. TTC typically affects aged postmenopausal women and is usually triggered by emotional or physical stress. The exact pathophysiology remains unknown but datas suggest a link between sympathetic hyperactivity (catecholamine plasmatic level, heart rate variability depressed) and TTC. Up to now, no direct evidence of sympathetic hyperactivity has been established.

The aim of our study was to determine, by microneurography (direct technique), if patients with TTC present an increased of muscle sympathetic nerve activity (MSNA) in TTC patients in comparison to matched heart failure controls.

We enrolled 13 TTC patients (80.1±2.1 years, all female, Body Mass Index: 22.8±0.9 kg/m², Left Ventricular Ejection Fraction: 40±2%) and 13 control patients matched for age, sex, BMI, LVEF, renal function and hemoglobinemia. Between 36 hours after admission, all patients underwent a microneurography and an arterial baroreflex gain assessment (slope of the relationship between MSNA and diastolic blood pressure).

There is no difference between groups on hemodynamics parameters (SBP, DBP, MBP and HR) and oxygen saturation. TTC patients presented a significant increase of sympathetic activity (66.3±2.7 vs 55.6±2.6 bursts/min; $p=0.0088$). Arterial baroreflex gain is significantly decreased compared to control patients (1.2±0.3 vs. 2.5±0.4 %MSNA/mmHg; $p=0.005$).

This study showed for the first time with a direct technique, that TTC patients present a sympathetic hyperactivity. The increase of sympathetic nerve activity is associated to a decrease of arterial baroreflex gain.